Remarks and Arguments

Claims 62 and 67 are under examination with the entry of this Amendment. Claim 62 has been amended to recite that the immune response induced by the method is against an influenza virus. Claims 64-65 and 68-70 have been canceled without prejudice. Claims 1-61, 63, and 66 have been canceled previously. No new matter has been introduced with this Amendment.

Claim Rejections under 35 U.S.C. 112:

Claims 62, 64-65, and 67-68 are rejected under 35 U.S.C. 112, first paragraph, as allegedly non-enabling. Applicants respectfully traverse this rejection.

The Office Action alleges that the Specification, while being enabling for using a formalin inactivated influenza virus P8/5 to induce a serum immune response in a CD4 T cell deficient mouse model, does not reasonably provide enablement for using any or all inactivated or attenuated virus to induce a serum immune response in a CD4+ T cell deficient animal and human.

Without acquiescing to this aspect of the rejection and in the interest of advancing prosecution of this application, claim 62 has been amended such that the method defined is for inducing an immune response against an influenza virus, not for any or all viruses, by using an inactivated intact influenza virus preparation.
Claims 64-65 and 68 have been canceled without prejudice.

The Office Action states that "the state of art indicate(s) that vaccination of immune compromised patients, such as HIV infection patients, is very unpredictable...." by citing Brichacek et al. The Office Action further states that "Brichacek et al. reported that vaccination of HIV positive patients with subunit Pneumococcal and influenza vaccine increase the plasma HIV viral load."

Applicants emphasize that the claimed method is useful for inducing an immune response in a subject who is deficient in CD4+ T cells. This invention is based on the actual experimental data described in the Specification, i.e., the administration of a formalin-inactivated influenza virus preparation induced antibody production in mice lacking CD4+ T cells and provided immune protection against influenza virus.

The relevance of the cited reference, Brichacek et al., is not clear. The statement quoted above that the vaccination of HIV positive patients with subunit Pneumococcal and influenza vaccine increase the plasma HIV viral load has little relevance for the claimed invention. The invention claimed is a method of inducing an immune response in a CD4+ T cell deficient subject. Amended claim 62 defines a method of inducing an immune response against an influenza virus in a subject who lacks CD4+ T cells. The HIV positive patients employed for the studies described in Brichacek et al. were not CD4+ T cell deficient as shown in Table 1. This is because the focus of their studies was to test the hypothesis that the replication of HIV-1 within CD4+ T lymphocytes is dependent upon the activation state of the cell and that the activation of T lymphocytes that accompanied the immune response to antigens directly enhances virus burden. The results of their studies support the hypothesis.

Based on the above, Applicants submit that the claim rejection under Section 112 as non-enabling based on Brichacek et al. is not proper and thus should be withdrawn.

Regarding the issues raised in item 4 on page 3 of the Office Action, Applicants submit that claim 62 has been amended in such a way that the issues are no longer applicable. With respect to the statement that "there is not enough evidence to support the broadly claimed invention, especially, it reads on a method for treating human beings...." Applicants submit that this allegation is not justified in the present case. MPEP 2164.02 specifically provides guidance for this issue, i.e., the relationship between *in vitro* or *in vivo* animal model assays and a disclosed or a claimed method of use. It is stated that "[A]n *in vitro* or *in vivo* animal model example in the Specification, in effect, constitutes a "working example" if that example "correlates" with a disclosed or

claimed method invention.... The issue of "correlation" is also dependent on the state of the prior art...." The claimed invention is based on the experimental data in mice lacking CD4+ T cells. There is no reason why one would not expect to be able to extrapolate the data disclosed in the Specification to the scope of the claims. Applicants submit that the Specification does provide sufficient enablement for using an immunogenic composition containing inactivated influenza viruses to induce an immune response against the influenza virus in a CD4+ T cell deficient animal or human. This is consistent with the court decision that "... the Examiner must ... decide whether one skilled in the art would accept the model as reasonably correlating to the condition." (Emphasis added.) *In re Brana* 34USPQ2d 1436. The Examiner is also reminded that "[A] rigorous or an invariable exact correlation is not required" as stated in Cross v. Iizuka 224USPQ739.

Claim Rejections under 35 U.S.C. 102:

Claims 62 and 67-69 are rejected under 35 U.S.C. 102(b) as allegedly anticipated by Levine et al. Applicants respectfully traverse this rejection.

Applicants emphasize that the claimed method is useful for inducing immune responses in a subject who is deficient in CD4+ T cells. This invention is based on the actual experiments in mice lacking CD4+ T cells. The prevailing theory in the field was that the CD4+ T cells are essential for inducing antibody production as discussed in the Specification (page 2, lines 26-28). Thus, the inventors' demonstration that the CD4+ T cell deficient mice can be protected against influenza virus by immunization with the immunogenic composition containing inactivated intact influenza virus was a surprising finding.

Levine et al. describe the studies directed to determine whether the development of AIDS in HIV-infected individuals is delayed or prevented by immunization with an inactivated HIV preparation (gp120-depleted HIV-1 immunogen).

With the entry of this Amendment, amended claim 62 defines a method for inducing an immune response against an influenza virus in a CD4+ T cell deficient subject using an inactivated influenza virus preparation as an immunogen. Accordingly, Levine et al. has no relevance for the invention. Levine et al. used HIV immunogen and the subjects employed for their studies were not CD4+ T cell deficient, as indicated in the abstract (lines 6-7) as well as in Tables 1 and 2. Therefore, the claimed invention is not anticipated by Levine et al.

Claim 70 is rejected under 35 U.S.C. 102(b) as allegedly anticipated by Jackson et al. Applicants respectfully traverse this rejection.

Without acquiescing to this aspect of the rejection and in the interest of advancing prosecution of this application, claim 70 has been canceled without prejudice. However, Applicants provide the following comments regarding the cited reference. Jackson et al. describe the effects of influenza immunization on immunological and virologic characteristics of HIV-infected children. The influenza vaccine used in their studies was a commercial split-virus vaccine manufactured by Wyeth-Ayerst. Attached herewith as Exhibit A is a copy of the product information of the influenza vaccine available on the web. Although this information is specific for the 2002-2003 formula of the influenza vaccine (the exact formula is updated each season depending on the type of the influenza virus prevalent during that particular season), it is sufficient to demonstrate the composition of the vaccine used in Jackson et al.; the vaccine contained purified subvirions of three types, i.e. hemagglutinin antigens of A/Texas H1N1, A/Shangdong H3N2 and B/Panama. Accordingly, Jackson et al. did not use the immunogenic composition containing an inactivated intact influenza virus as is the case with the present invention. Furthermore, the pediatric patients employed in Jackson et al. studies did not lack CD4+ T cells as evidenced by the statement that the CD4+ counts were not significantly different before and after immunization (see abstract on page 200) and the data in Fig. 1.

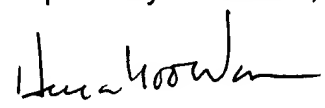
Based on the above, Applicants submit that the invention as claimed is not anticipated by either Levine et al. or Jackson et al. Withdrawal of the rejection under 35 U.S.C. 102 is respectfully requested.

Conclusion:

Based on the foregoing amendments and arguments, this case is considered to be in condition for allowance and passage to issuance is respectfully requested.

It is believed that this amendment does not necessitate the payment of any additional fees under 37 C.F.R. 1.16-1.17. If this is incorrect, please charge any amount due to Deposit Account No. 07-1969.

Respectfully submitted,



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PDR Drug information for

PDR® entry for

INFLUENZA VIRUS VACCINE, (Wyeth-Ayerst)
Trivalent, Types A and B (Purified Subvirion)
FLUSHIELD®
2002-2003 Formula
DO NOT INJECT INTRAVENOUSLY<Rx only

DESCRIPTION

FluShield ® (Influenza Virus Vaccine, Trivalent, Types A and B [Purified Subvirion]) is a sterile injectable for administration intramuscularly.

FluShield is prepared from the allantoic fluids of chick embryos inoculated with a specific type of influenza virus. During processing, not more than 500 µg of gentamicin is added to each embryonated chicken egg. The harvested virus is concentrated, purified, then inactivated with formaldehyde.

The viral antigens contained in FluShield, Trivalent(Purified Subvirion) are concentrated and refined by a column-chromatographic procedure. At the same time, addition of tri(n) butylphosphate and Polysorbate 80, USP, to the column-eluting fluids effects inactivation and disruption of a significant proportion of the virus to smaller subunit particles. The recovered subvirion (split-virus) suspension is freed of substantial portions of the disrupting agents by resin treatment and of other undesirable materials by dialysis through membranes of controlled pore size.

The viral antigen content has been standardized by immunodiffusion tests, according to current U.S. Public Health Service (PHS) requirements. Each dose (0.5 mL) contains the proportions and not less than the microgram amounts of hemagglutinin antigens (µg HA) representative of the specific components recommended for the 2002-2003 season: 15 µg HA of A/New Caledonia/20/99 (H1N1), 15 µg HA of A/Panama/2007/99 (H3N2) (A/Moscow/10/99 [H3N2]-like), and 15 µg HA of B/Hong Kong/330/2001.